REMARKS

Claims 66, 71, 72, 86-88, 91 and 105-108 are all the claims pending in the application. Claims 66, 71, 72, 86, 87, 91 and 106-108 have been rejected. Claim 105 is objected to. Claim 88 is allowed.

Claim 71 is being cancelled herein. Claims 66 and 88 are being amended.

No new matter had been added. Entry of this amendment is respectfully request.

I. Claim Objections

A. At paragraph 5 of the Office Action, the Examiner notes that if claim 71 is found to be allowable, claim 106 will be objected to as being a substantial duplicate thereof.

Included herewith is an amendment to the claims, canceling claim 71. In view of the cancellation of claim 71, the instant objection is moot and Applicants respectfully request reconsideration and withdrawal of this objection.

B. At paragraph 6 of the Office Action, claim 88 is objected to under 37 C.F.R. §1.75 as being a substantial duplicate of claim 105.

Included herewith is an amendment to claim 88, such that the claim now recites an polypeptide that "consists of" SEQ ID NO:2. As the scope of claim 88, as amended, is different from that of claim 105, the claims are not substantial duplicates of each other. Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

II. Rejection of claims under 35 U.S.C. §112, first paragraph

A. At paragraph 7 of the Office Action, the rejection of claim 72 under 35 U.S.C. §112, first paragraph, as lacking adequate written description, has been maintained by the Examiner for the reasons of record, namely, that the specification fails to describe a

representative number of species of the genus of claimed polypeptides, which encompasses widely variant species with respect to structure and/or function.

The Examiner states that the genus of polypeptides comprising SEQ ID NO:6 of the composition of claim 72 encompasses species that are widely variant, citing as an example the polypeptide of O'Donnell et al (cited in a previous Office Action). The Examiner notes that the genus recited in claim 72 encompasses all species of polypeptides that comprise SEQ ID NO:6, i.e., those having SEQ ID NO:6 and additional structural features. The Examiner concludes that the single representative species of SEQ ID NO:2 fails to represent all species encompassed by the genus.

Applicants respectfully traverse the Examiner's position that the claim lacks adequate written description support in the specification as filed.

In the present application, *inter alia*, Applicants describe the characterization of a novel *Staphylococcus aureus* polypeptide STAAU_R9 (SEQ ID NO:2) that has been shown to bind to a specific bacteriophage polypeptide (SEQ ID NO:4). Binding of the bacterial polypeptide by the bacteriophage polypeptide has a cytotoxic effect on bacteria expressing the bacteriophage polypeptide. Applicants have also identified the minimal binding domain (SEQ ID NO:6) necessary for interaction of the full-length bacterial polypeptide with the bacteriophage protein (see Figure 10).

Claim 72 of the instant application recites a composition comprising the minimal binding domain of SEQ ID NO:2 (i.e., SEQ ID NO:6) and the bacteriophage polypeptide of SEQ ID NO:4. This composition can be used, for example, to screen for candidate compounds that bind SEQ ID NO:2, or that block the interaction between SEQ ID NO:2 and SEQ ID NO:4.

The Examiner states that the claim recites a genus of widely variant species (where the genus is represented by a "polypeptide comprising SEQ ID NO:6") and that Applicants have only provided one example of the genus (SEQ ID NO:2). Applicants respectfully note that in contrast to the Examiner's position, the genus is not widely variant. It comprises only those polypeptides that include SEQ ID NO:6 and that bind to SEQ ID NO:4. The skilled artisan would readily understand the characteristics of a member of this genus.

Applicants also respectfully note that the examples provided in the instant application include additional examples of the claimed genus. As shown in Figure 10, there are seven polypeptides that comprises SEQ ID NO:6, each of which were shown to have the ability to bind SEQ ID NO:4. Those proteins encompasses the following residues of SEQ ID NO:2: 1-599, 35-599, 229-599, 380-599, 449-599, 490-599, 530-599.

Regarding the Examiner's comments about the polypeptide of O'Donnell at page 4 of the Action, Applicants understand the Examiner to be stating that because the polypeptide of O'Donnell is structurally different from SEQ ID NO:2 while comprising SEQ ID NO: 6, the polypeptide of O'Donnell is an example of a "species" failing to have the claimed properties (i.e., binding a polypeptide comprising SEQ ID NO:4). For the record, the Applicants wish to note that they not stated or suggested that the polypeptide of O'Donnell would not bind to SEQ ID NO:4. To the contrary, it is highly expected that the polypeptide of O'Donnell would bind to SEQ ID NO:4 because it has a relatively high homology to SEQ ID NO: 2 and because it contains the binding domain of SEQ ID NO: 6.

Applicants note that in the last line of paragraph 7 of the Office Action, the Examiner comments that SEQ ID NO:6 is "only a minimal portion of the representative polypeptide of

SEQ ID NO:2, which is 599 amino acids in length, and consequently this fragment of SEQ ID NO:2 fails to constitute a substantial portion of the genus of claimed polypeptides comprising SEQ ID NO:6 of the composition of claim 72."

Applicants understand the Examiner to be stating that because of its relatively small size (39 amino acids), as compared to the full-length protein (599 amino acids), SEQ ID NO:6 fails to constitute a substantial portion of the claimed polypeptide comprising SEQ ID NO:6 of the claim. This argument is unfounded because the Examiner has not shown any evidence of an inverse correlation between the size of a protein fragment and the likelihood of that fragment to be a representative of a class. To the contrary, it is well known that highly conserved or essential domains of proteins (e.g., zinc-finger domains, catalytic domains, etc.) generally represent only a minimal portion of the full-length protein.

If, instead, the Examiner is stating that SEQ ID NO:6 itself fails to constitute a substantial number of the claimed polypeptides that contain SEQ ID NO:6, Applicants agree that SEQ ID NO:6 alone, without modification, would only be one member of the genus of polypeptides recited in the claim. However, as recited in the claim, all members of the genus of polypeptides comprising SEQ ID NO:6 would contain SEQ ID NO:6, and only those members binding specifically to a polypeptide comprising SEQ ID NO:4 are encompassed by the claim. Beyond this, the point of the Examiner's statement is unclear. If the Examiner is referring to the possible inability of SEQ ID NO:6 to bind to SEQ ID NO:4, the Examiner's attention is drawn to Figure 10 of the specification, providing experimental results demonstrating the binding activity of SEQ ID NO:6.

In view of the points above, it is clear that there is adequate written description support for claim 72 in the specification. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

B. At paragraph 8 of the Office Action, the rejection of claims 66, 71-72, 86-87, 91 and 106-108 under 35 U.S.C. §112, first paragraph, has been maintained for the reasons of record, namely, that while the specification is enabling for the isolated polypeptide of SEQ ID NO:2, it does not reasonably provide enablement for the full scope of the claimed polypeptides.

Applicants respectfully traverse the Examiner's position for the following reasons.

To satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and use the claimed subject matter without undue experimentation. The law does not require "a specific example of everything within the scope of a broad claim." *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973); *See also In re Grimme, Keil and Schmitz*, 124 USPQ 449, 502 (CCPA 1960) ("it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.").

Thus, there is no requirement for disclosure of every species within a genus. An applicant may include claims in his application that encompass in scope not only that which applicant has

specifically exemplified, but also that which the skilled artisan could obtain based on the teachings of the applicants and the knowledge of the art.

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is not whether any experimentation is necessary, but whether, if experimentation is necessary, whether it is undue. *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *In re Wands*, 858 F.2d 173, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

With regard to the specific claims included in the rejection, Applicants note that the claims recite two groups of polypeptides, based both on structural and functional characteristics. The first group of polypeptides (claims 66, 72 and 106) are those comprising SEQ ID NO:6, the minimal binding domain of the full-length bacterial primase set forth in SEQ ID NO:2. As recited in the claims, this group of polypeptides is defined based on structure in that each member of the genus must contain SEQ ID NO:6. This group of polypeptides is also defined based on function in that each member of the genus must have the ability to bind to SEQ ID NO:4, the bacteriophage polypeptide shown by Applicants to bind both the full-length polypeptide (SEQ ID NO:2) and the minimal binding domain (SEQ ID NO:6).

The second group of polypeptides (claims 86-87, 91, 107 and 108) are those comprising SEQ ID NO:2 (the full-length bacterial primase), consisting of SEQ ID NO:2, and sequence variants of SEQ ID NO:2. As recited in the claims, this group of polypeptides is defined based

on structure in that each member of the genus must either contain SEQ ID NO:2, or be a very close sequence variant of SEQ ID NO:2. This group of polypeptides is also defined based on function in that each member of the genus must either have the ability to bind to SEQ ID NO:4 or have one of the enzymatic activities set forth in the claims.

Thus, the claims are not directed to *any* polypeptide, but to a well-defined group of polypeptides having shared structure and function. The skilled artisan would clearly understand the scope of the invention based on the claims, and would be able to easily make and use a polypeptide falling within the scope of the claims. The skilled artisan would utilize the information provided in the specification to obtain a polypeptide having one of the activities recited in the claims (e.g., SEQ ID NO:2), and then make modifications to the active polypeptide to determine the effects of such changes on the active polypeptide. The results of such experiments would allow the artisan to quickly determine specific alternations that may be made, such that a determination can be made as to whether the altered polypeptide remains within the scope of the claims. The Examiner appears to be addressing the invention from the standpoint of one starting from "scratch", i.e., without an active polypeptide and without the information that the minimal binding domain is SEQ ID NO:6.

As noted above, the standard for undue breadth of claims is whether it would require undue experimentation to practice what is claimed. Applicants respectfully assert that it would not require undue experimentation to practice what is being claimed, i.e., polypeptides defined both by structure and function.

For example, claim 66 recites a polypeptide comprising amino acids 380 to 599 of SEQ ID NO:2 that has the ability to bind to a polypeptide comprising SEQ ID NO:4. As shown in the

results exemplified in Figure 10 of the instant application, a polypeptide consisting of amino acids 380 to 599 of SEQ ID NO:2 is able to bind to SEQ ID NO:4. As also shown in Figure 10, larger polypeptides comprising amino acids 380 to 599 of SEQ ID NO:2 (i.e., amino acids 1-599, 35-599, and 229-599) are also able to bind to SEQ ID NO:4. It would not require undue experimentation for the skilled artisan to make other species of polypeptides that fall within the scope of this claim, and to test such polypeptides for activity. Indeed, one would merely need to select a polypeptide comprising at least amino acids 380 to 599 of SEQ ID NO:2, and then assay for the ability of the candidate to bind to SEQ ID NO:4. A number of non-limiting methods useful to measure the binding between polypeptides of the present invention are described at pages 22-23 and 78-83 of the specification. For instance, binding can be measured by coupling one molecule to a surface or support (such as a membrane, a microtiter plate well, or a microarray chip), and monitoring binding of a second molecule by any number of means including, but not limited to, optical spectroscopy, fluorometry, and radioactive label detection. A detailed experimental protocol for testing binding activity is also provided in Example 3 of the instant application.

Claim 72 is similar to claim 66, with the main modification being the use of a smaller fragment of SEQ ID NO:2. Again, as shown in Figure 10, this smaller fragment, namely, SEQ ID NO:6, has the ability to bind to SEQ ID NO:4. Seven examples of polypeptides comprising SEQ ID NO:6, and thus falling within the scope of the claim, are also shown in Figure 10. As with claim 66, it would not be undue experimentation for the skilled artisan to make other species of polypeptides that fall within the scope of the claims, and to test such polypeptides for their ability to bind SEQ ID NO:4, using the methods described above.

For these same reasons, it would not be undue experimentation for the skilled artisan to make and use the polypeptides that fall within the scope of claim 106.

Claims 86-87, 91, 107 and 108 recite a small genus of polypeptides, well defined by their structure and activity. Indeed, the claims are limited to those polypeptides that have at least 95% identity or 97% similarity over their entire length to SEQ ID NO:2. This genus of polypeptides is quite small, encompasses only those polypeptides having a small number of amino acid alternations. Again, specific activities for these polypeptides are also recited in the claims, namely, the ability to bind to a polypeptide comprising SEQ ID NO:4 or having one of the activities recited in the claims (see., e.g., claims 91, 107 and 108).

As with the polypeptides comprising the fragment of SEQ ID NO:2 discussed above, the skilled artisan could easily envision a polypeptide falling within the scope of the claim, and test the polypeptide for the activity recited in the claims. It would not require undue experimentation to make and use the invention recited in these claims. An experimental protocol for testing binding activity is provided in Example 3 of the instant application, and additional means provided in the specification are discussed above.

In addition, Applicants note that claims 86-87, 91, 107 and 108 recite subject matter that the U.S. PTO has used in an example of its Written Description Guidelines. Example 14 of the Guidelines cites approvingly to a claim reciting a polypeptide comprising a specific identifier (SEQ ID NO:3) and variants thereof having 95% identity. The claim also defines the recited polypeptides by function. In the instant application, claims 86-87, 91, 107 and 108 similarly recite polypeptides comprising at least 95 % identity (or 97% similarity) and a specific function. While Applicants recognize that Example 14 is in the Written Description Guidelines, and the

instant rejection is one of enablement, Applicants note that in the "Analysis" of Example 14, it is stated that

> The procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.

It is clear that the U.S. PTO views claims to polypeptides and their variants (having at least 95% identity), that include a recitation of activity, to be fully enabled.

As claims 86-87, 91, 107 and 108 of the instant application are of the same or narrower scope as the claim in Example 14, and because the specification provides methods for use in identifying proteins having the claimed activities as discussed above, claims 86-87, 91, 107 and 108 are also enabled.

As to the Examiner's arguments set forth in the Office Action, Applicants have the following comments.

In the second paragraph of page 5 of the Office Action, the Examiner states "Applicants have *allegedly* identified amino acids 561-599 of the *S. aureus* polypeptide of SEQ ID NO:2 as being required for binding of SEQ ID NO:2 to SEQ ID NO:4" (emphasis is ours). Applicants note that the results of experiments demonstrating that amino acids 561-599 are, in fact, required for binding of SEQ ID NO:2 to SEQ ID NO:4, are provided in the specification, and exemplified in Figure 10. Accordingly, the Examiner is respectfully requested to clarify his comment.

At the bottom of page 5 of the Office Action, the Examiner states that the polypeptides of claims 91 and 107-108 are not limited to those that bind SEQ ID NO:4, and it would be unclear

how a skilled artisan would use polypeptides that do not have the ability to bind SEQ ID NO:4. Applicants note that claims 91 and 107-108 recite other activities for the polypeptides encompassed within the scope of the claims. Thus, the invention is not limited to only those polypeptides that bind SEQ ID NO:4, but instead includes those polypeptides having enzymatic activities. A number of non-limiting assays useful to measure the biological activity of polypeptides of the present invention are described at pages 23-26 and 84-89 of the specification. For instance, suitable assays include measurement of the stimulation of DNA synthesis, DNA-dependent RNA polymerase activity, stimulation of DNA unwinding activity by DNA helicase and stimulation of DNA helicase ATPase activity.

Near the top of page 6 of the Office Action, the Examiner states that claims 86-87, 91 and 107-108 are not limited to polypeptides comprising the minimal binding domain of SEQ ID NO:2 (e.g., SEQ ID NO:6) and that the specification provides no guidance as to amino acids of SEQ ID NO:2 that can be altered with an expectation of maintaining binding activity. While the Examiner contends that the experimentation required to determine which alterations could be made without affecting the binding ability of the claim polypeptides would be undue, Applicants respectfully disagree. The skilled artisan could readily make polypeptides, falling within the limited scope of the claims, and test them for binding activity with SEQ ID NO:4. No special technical knowledge would be required to make altered proteins and test them for activity, and thus such experimentation would be routine. As mentioned hereinbefore, a number of non-limiting methods useful to measure the binding between polypeptides of the present invention are described at pages 22-23 and 78-83 of the specification and an experimental protocol for testing binding activity is provided in Example 3 of the instant application.

The Examiner goes on, at the bottom of page 6, to argue that "one of skill in the art would recognize [the minimal binding fragment of SEQ ID NO:2 (i.e., SEQ ID NO:6)] as likely being exposed at the surface of the polypeptide, i.e., not buried within the core of the protein." The Examiner further states that there is no evidence of record to suggest that when the minimal binding domain of SEQ ID NO:2 is "internalized" within a polypeptide sequence that such polypeptides would also have the ability to bind SEQ ID NO:4. The Examiner concludes that it is highly unpredictable as to whether all polypeptides comprising the recited fragments of SEQ ID NO:2 would bind to SEQ ID NO:4.

Applicants first note that "official notice unsupported by documentary evidence should only be taken by the Examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known." MPEP 2144.03, citing *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970) which further stated that the notice of facts beyond the record must be "capable of such instant and unquestionable demonstration as to defy dispute." Applicants respectfully assert that the location of the binding domain of all proteins would not be a fact of "instant and unquestionable demonstration as to defy dispute."

Therefore, the Examiner has provided no evidence that the placement of the minimal binding domain in a larger protein would result in a polypeptide lacking the ability to bind SEQ ID NO:4. Moreover, it would not require undue experimentation for the skilled artisan to test a candidate protein for it's ability to bind SEQ ID NO:4. A number of methods useful to measure the binding between polypeptides of the present invention are described at pages 22-23 and 78-

83 of the specification, and an experimental protocol for testing binding activity is provided in Example 3 of the instant application.

The Examiner notes in the middle of page 7 of the Office Action that the specification fails to identify the region of SEQ ID NO:4 that interacts with SEQ ID NO:2. The Examiner again comments on the likelihood of the location of the binding region of SEQ ID NO:4 being at the amino or carboxy terminus of SEQ ID NO:4, and states that it would be highly unpredictable as to whether the claimed polypeptides would interact with a polypeptide *comprising* SEQ ID NO:4.

Applicants note that the Examiner has provided no evidence to support his position regarding the likely location of the binding region of SEQ ID NO:4.

In addition, as with SEQ ID NO:2, it is evident that the skilled artisan would be able to select a polypeptide comprising SEQ ID NO:4 and test it for binding activity with a polypeptide corresponding to SEQ ID NO:2 of the claims. Once again, a number of methods useful to measure the binding between polypeptides of the present invention are described at pages 22-23 and 78-83 of the specification and an experimental protocol for testing binding activity is provided in Example 3 of the instant application.

The Examiner goes on to comments on the unpredictability of the effects of altering the sequence of SEQ ID NO:2. Applicants reiterate that it would not require undue experimentation to make and test the polypeptides falling within the scope of the claims. Applicants provide ample references on how such might be done in the specification, as discussed above.

The Examiner concludes on page 8 by noting that one of skill in the art would need to make all polypeptides as broadly encompassed by the claims, screen those that have the ability to

bind SEQ ID NO:4 and further screen those polypeptides that have the ability to inhibit growth of *S. aureus*. Applicants respectfully note that the none of the claims include a limitation that the polypeptides recited in the claims must have the ability to inhibit growth of *S. aureus*.

Finally, Applicants note that the references relied upon by the Examiner to support his position are irrelevant in the instant case. The references relied upon by the Examiner concerns antibodies. Applicant is not claiming antibodies but *S. aureus* polypeptides, fragments and variants whose functions, structures and activities in other species are well-known (see list of references provided at pages 11 to 13 of the Response filed September 1, 2004).

Applicants further note that the references relied upon by the Examiner to support his position were published in 1992 and 1996. Such references do not establish the state of the art at the time of effective filing date of the instant application in 2000. There has been a tremendous increase in knowledge since 1992 and 1996. One of skill in the art in 2000, with the advances in bioinformatics, high-throughput screening, robotics, automatic peptide synthesis and analysis and the ability to model protein structures, could have assessed and identified modifications that alter binding capacities. One skilled in the art would also have had little difficulty in assessing and identifying modifications that would alter the regular activity of the primase polypeptide, especially since important domains for bacterial primase activity were published and known to those of skill in the art (see again list of references provided at pages 11 to 13 of the Response filed September 1, 2004). Furthermore, truncation and modification of polypeptides are routinely performed in this art.

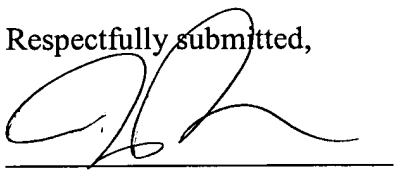
For all the reasons discussed above, Applicants respectfully assert that the claims cited by the Examiner are fully enabled, and therefore respectfully request reconsideration and withdrawal of this rejection.

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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